THE MECHANISM OF THE ANOMALOUS CLEMMENSEN REDUCTION OF BICYCLIC AMINOKETONES POSSESSING A BRIDGEHEAD NITROGEN

BY

WILLIAM COOPER WILDMAN

A.B., DePauw University, 1943
M.S., University of Illinois, 1947

AN ABSTRACT OF A THESIS

SUBMITTED IN PARTIAL FULFILLMENT OF THE REQUIREMENTS
FOR THE DEGREE OF DOCTOR OF PHILOSOPHY IN CHEMISTRY
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Introduction

Clemmensen reduction of 1-ketoquinolizidine occurs with a concurrent rearrangement of the ring structure. The product, 1-azabicyclo[5.3.0]decane, has been synthesized unequivocally (1), but no definite mechanism has been proposed for this unusual rearrangement. The primary object of this investigation was to establish which ring of the bicyclic aminoketone underwent contraction. This was accomplished by the synthesis of 8-methyl-1-azabicyclo[5.3.0]decane and 4-methyl-1-azabicyclo[5.3.0]decane. Since Clemo (2,3) has reduced 1-keto-2-methylquinolizidine and 1-keto-8-methylquinolizidine under Clemmensen conditions, either 8-methyl-1-azabicyclo-[5.3.0]decane or 4-methyl-1-azabicyclo[5.3.0]decane must be the rearranged, reduced product of each aminoketone.

With this knowledge as a foundation, Clemmensen reductions of the structurally related bicyclic aminoketones, 6-keto-1-azabicyclo[5.3.0]decane and 1-keto-3-methylpyrrolizidine, were performed to determine the scope of the reduction-rearrangement and a more precise mechanism for it.

Discussion Of Results

The synthesis of 8-methyl-1-azabicyclo[5.3.0]decane and 4-methyl-1-azabicyclo[5.3.0]decane was accomplished by a modification of the general procedure which Prelog and co-workers originated (1,4,5). The method was checked by using the preparation of the known 1-azabicyclo[5.3.0]decane as a control synthesis. The fundamental starting material for this synthesis, 1,9-*bis*-(*p*-methoxyphenoxy)-4-nonanone, was prepared by the action of the Grignard reagent of 1-chloro-5-(*p*-methoxyphenoxy)-pentane on 1-cyano-3-(*p*-methoxyphen-

oxy)-propane. The halide precursor of the Grignard reagent was synthesized by the monocondensation of hydroquinone monomethyl ether with 1,5-dichloropentane; the nitrile was prepared by a method described for the phenoxy analog (6). The ketone was subjected to catalytic reductive amination to yield the primary amine. The ether groups then were removed with hydrobromic acid to form the 1,9-dibromoamine hydrobromide, which was converted to the bicyclic amine by intramolecular dialkylation in dilute aqueous sodium hydroxide.

By repeating the control synthesis using the properly substituted ketones, the unequivocal preparation of 8-methyl-1-azabicyclo[5.3.0]decane and 4-methyl-1-azabicyclo[5.3.0]-decane was achieved.

A comparison of the melting points of the derivatives of 8-methyl-1-azabicyclo[5.3.0]decane and 4-methyl-1-azabicyclo-[5.3.0]decane with those reported by Clemo from the Clemmensen reduction of 1-keto-2-methylquinolizidine and 1-keto-8-methylquinolizidine showed that reduction of 1-ketoquinolizidines proceeds with ketonic ring contraction.

The synthesis of 6-keto-1-azabicyclo[5.3.0]decane was achieved by the Dieckmann ring closure of ethyl δ-N-(2-carbethoxypyrrolidyl)-valerate, followed by hydrolysis and decarboxylation. The diester was obtained by ethanolysis of δ-N-(2-carbethoxypyrrolidyl)-valeronitrile, the product of the condensation of ethyl proline with δ-bromovaleronitrile. Clemmensen reduction of 6-keto-1-azabicyclo[5.3.0]decane gave the rearranged product, quinolizidine, while Wolff-Kishner reduction gave the normal product, 1-azabicyclo-[5.3.0]decane.

The synthesis of 1-keto-3-methylpyrrolizidine was accomplished by the Dieckmann ring closure of ethyl β-N-(2-carbethoxypyrrolidyl)-butyrate, product of the condensation of ethyl proline with ethyl crotonate. The intermediate ketoester was not isolated, but was hydrolyzed and decarboxylated to yield the aminoketone. Wolff-Kishner reduction of 1-keto-3-methylpyrrolizidine formed the normal reduced product,

3-methylpyrrolizidine. Only one product could be isolated from the Clemmensen reduction of 1-keto-3-methylpyrrolizidine, namely 3-methylpyrrolizidine.

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VITA

The author was born in Oak Park, Illinois, on March 20, 1923. He attended the public schools there and was graduated from the Oak Park and River Forest Township High School in June, 1940. He entered DePauw University in September, 1940, and received the degree of Bachelor of Arts from that school in December, 1943. During the period from September, 1943, to April, 1944, he was an assistant in teaching and research in organic chemistry at DePauw University. From 1944 to 1946, he served in the United States Navy. He entered the Graduate College of the University of Illinois in June, 1946, and received the Master of Science degree in June, 1947. He held University fellowships from September, 1947, to June, 1949, and a research grant from the Research Board of the University of Illinois during the summer of 1948.

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